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10/525,821	02/25/2005	Joachim Kralik	MERCK-2978	9167

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MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201

EXAMINER

CUTLIFF, YATE KAI RENE

ART UNIT	PAPER NUMBER
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1621

MAIL DATE	DELIVERY MODE
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08/06/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/525,821	Applicant(s) KRALIK ET AL.	
	Examiner Yate K. Cutliff	Art Unit 1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 April 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-14 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-14 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date: <u>1: 7/18/2007</u> |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>02/25/2005</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II, claims 1-14 drawn to the process for preparation of amino alcohol, claim 5 (in part) and not covered by Group I, wherein:

- R1, is a heterocyclic radical such as 2-thienyl, as defined in claim 2,
- R2 is a methyl as defined in claim 3,
- n is 1 as defined by claim 4,
- the catalyst of formula A is a transition-metal complex containing rhodium or salts thereof as defined in claim 7, and species A, the transition metal complexed to the ligand according to formula A of claims 1, 6 and 7; in the reply filed on April 30, 2007 is acknowledged. Further, pursuant to an Examiner initiated telephonic interview, held July 3, 2007 applicant elected, with traverse Ligand A (S)-Tol BINAP (see page 20 line 12) and a rhodium salt of the formula $[\text{Rh}(\text{COD})\text{Cl}]_2$. (see page 15 line 13).

The traversal is on the ground(s) that the full scope of the claims have unity of invention because they all share the same special technical feature, e.g., a process for the preparation of amino alcohols according to formula I by enantioselective hydrogenation of amino ketones of the formula II in the presence of a catalyst of formula A.

This is not found persuasive because the process as taught in Applicant's claim 1 is disclosed by the reaction set out in G. Helmchen et al.: "Houben-Weyl Methods of Organic Chemistry; Additional and Suppl. Vol. to the 4th ED." Vol. E 21 D,

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Stereoselective Synthesis (Pages 3955-3957, Chapter 2.2.1.2.7) 30 November 1995 (1995-11-30), George Thieme Verlag, Stuttgart - New York. The basic process is known and the variety of substituents for the R1 – R12 do not allow for the amino alcohols produced to have significant structural elements that can be shared by all derivatives. Additionally, the process is affected by the moieties of the R substituents.

The requirement is still deemed proper and is therefore made FINAL.

Priority

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 371 as follows:

Applicant failed to amend the first sentence(s) of the specification or an ADS in compliance with 37 CFR 1.78(a). See MPEP § 201.11.

If applicant desires to claim the benefit of a prior-filed application under 35 U.S.C. 371, a specific reference to the prior-filed application in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the title or in an application data sheet. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications.

It is noted that the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if

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the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Specification

3. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.
4. The disclosure is objected to because of the following informalities: it is not clear whether the Title is underlined or has been crossed out.

Appropriate correction is required.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

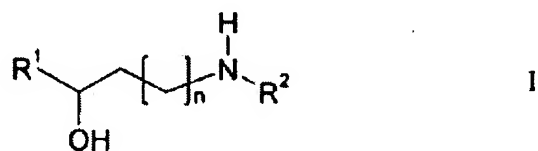
A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

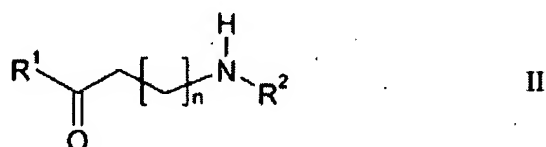
6. Claims 1 – 3, 6, 7, and 10 - 14 are rejected under 35 U.S.C. 102(b) as being anticipate by G. Helmchen et al.: "HOUBEN-WEYL Methods of Organic Chemistry; Additional and Suppl. Vol. to the 4th ED." Vol. E 21 D, Stereoselective Synthesis (Pages 3955-3956, Chapter 2.2.1.2.7) 30 November 1995 (1995-11-30), George Thieme Verlag, Stuttgart - New York.

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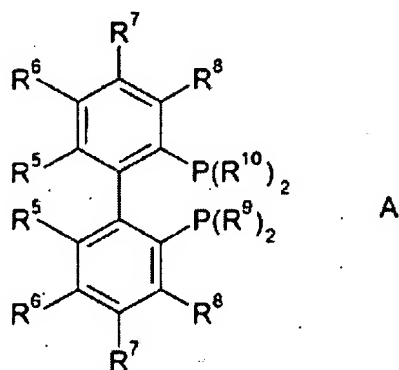
Applicant claims the process for enantioselective preparation amino alcohols of formula I



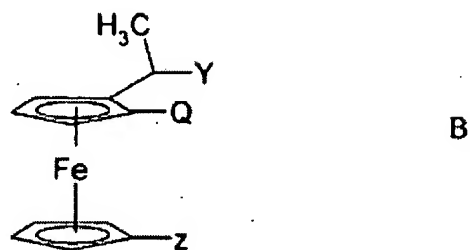
by enantioselective hydrogenation of amino ketones of formula II



with R1 - R-4, and n as defined in claim 1, in the presence of a non-racemic catalyst, characterized in that the catalyst is a transition-metal complex in which the transition metal is complexed to a chiral diphosphine ligand A as set out below:



with R5 - R12, and m as defined in claim; or ligand B as set out below:



with Q, Y and Z as defined in claim 1.

Reject claim 2 discloses that R1 denotes phenyl or 2-thienyl.

Rejected claim 3 discloses that R2 denotes methyl, ethyl, n-propyl or isopropyl.

Rejected claim 6 discloses that the chiral, non-racemic catalyst is a transition-metal complex containing one or more metals or salts thereof selected from the group consisting of rhodium, iridium, ruthenium and palladium.

Rejected claim 7 discloses that the chiral, non-racemic catalyst is a transition-metal complex containing rhodium or salts thereof.

Applicant, in Claim 10 states that the process for the preparation of compounds of the formula I has a reaction temperature is between 0 and 200°C.

Claim 12 discloses that the process for the preparation of compounds of the formula I has the hydrogenation carried out under 1-200 bar of hydrogen.

Claim 13 discloses that the process for the preparation of compounds of the formula I has the hydrogenation being carried out in the presence of an alcohol.

Claim 14 discloses that the process for the preparation of compounds of the formula I that the chiral, non-racemic catalyst is a transition-metal complex containing

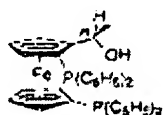
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sulfate, chloride, bromide, iodide, PF₆, BF₄, methanesulfonate, toluenesulfonate, hexachloroantimonate, hexafluoroantimonate or trifluoromethanesulfonate as anion.

Helmchen et al. teaches a process that involves the hydrogenation of alpha-amino ketones that results in the formulation of alpha-amino alcohol. The process is set out below:



where the catalyst is transition-metal complex comprised of a rhodium salt complexed to the ligand BPPFOH as follows:



Helmchen et al. discloses the use of catalyst, which are transition metal complexed to a chiral diphosphine ligand. Helmechen et al. at Table 6, the sixth and seventh position for R1 on the table, discloses a reaction that reads on Applicant's process. Specifically, where Applicant's R2 is either H or 1-20 C, n = 0 and R1 is an aromatic carbocyclic poly substituted by R3 and/or R4; with R3 and R4 defined as OH, or alkoxy. Further, Helmchen et al. discloses that the reaction is carried out in the presence of an Alcohol. (see Table 6). In Helmchen et al. teaches that a reaction temperature for the hydrogenation process is 20°C and the hydrogen pressure being 50 bar. (see Table 6). Lastly, the substrate/catalyst ration is 100:1. (see Table 6).

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Therefore, the process of claims 1 – 3, 6, 7, and 10 - 14 are anticipated by the reference.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

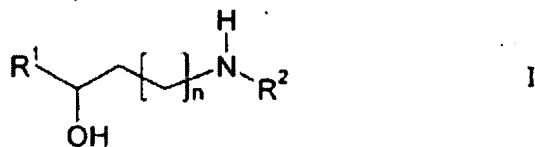
9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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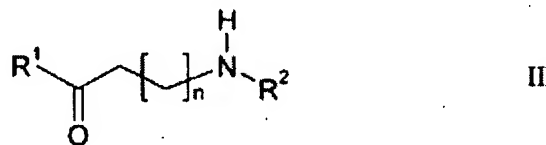
10. Claims 1, 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over G. Helmchen et al.: "HOUBEN-WEYL Methods of Organic Chemistry; Additional and Suppl. Vol. to the 4th ED." Vol. E 21 D, Stereoselective Synthesis (Pages 3955-3956, Chapter 2.2.1.2.7) 30 November 1995 (1995-11-30), George Thieme Verlag, Stuttgart - New York, in view of Sakurba et al. "Efficient Asymmetric Hydrogenation of γ -Amino Ketone Hydrochloride Derivatives catalyzed by (2S,4S)-4-Dicyclohexylphosphino-2-diphenylphosphinomethyl-1(N-methylcarbamoyl)-pyrrolidine(MCCPM)-Rhodium Complex", Synlett, October 1992, page 829, column 2, 17-19 and table 1 entry 8 (Sakurba 92); and further in view of Sakurba et al. "Efficient Asymmetric Hydrogenation of β - and γ -Amino Ketone Derivatives leading to practical Synthesis of Fluoxetine and Eprozinol", Chemical Pharmaceutical Bulletin 1995, page table 1, entry 4 and table 2 entry 8 (Sakurba 95).

Applicant Claims

Applicant claims the process for enantioselective preparation amino alcohols of formula I

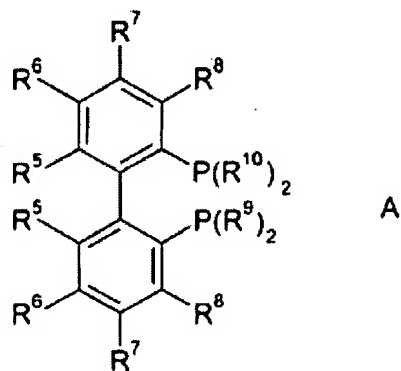


by enantioselective hydrogenation of amino ketones of formula II

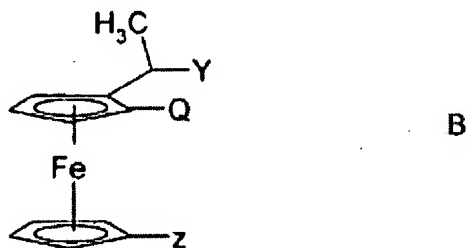


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with R1 - R-4, and n as defined in claim 1, in the presence of a non-racemic catalyst, characterized in that the catalyst is a transition-metal complex in which the transition metal is complexed to a chiral diphosphine ligand A as set out below:



with R5 – R12, and m as defined in claim; or ligand B as set out below:



with Q, Y and Z as defined in claim 1.

Rejected claim 4 discloses a process of claim 1 where n = 1.

Rejected claim 5 discloses a process of claim 1 where (Original) Process according to Claim 1 for the preparation of (S)-3-methylamino- 1 -phenyl- 1 -propanol or (S)-3-methylamino- 1-(2-thienyl)- 1 -propanol or acid-addition salts thereof.

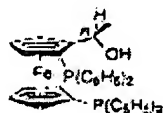
Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

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Helmchen et al. teaches a process that involves the hydrogenation of alpha-amino ketones that results in the formulation of alpha-amino alcohol. The process is set out below:

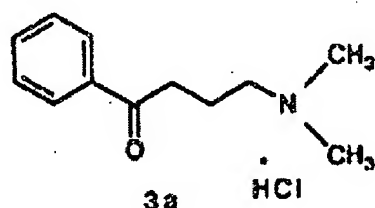


where the catalyst is transition-metal complex comprised of a rhodium salt complexed to the ligand (R)(S)-BPPFOH as follows:



Helmchen et al. discloses the use of catalyst, which are transition metal complexed to a chiral diphosphine ligand.

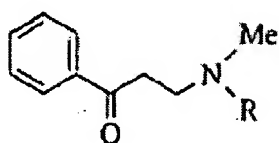
Sakurba 92, discloses the process for preparing amino alcohols by taking an alpha-amino ketone of the following formula:



and using a hydrogenation process catalyzed by a chiral bisphosphine ligand-rhodium(i) complex. Skurba 1 notes that the ligand (R)(S)-BPPFOH(5) complexed with $[\text{Rh}(\text{COD})\text{Cl}]_2$, was ineffective for the hydrogenation of the 3a.

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Sakurba 95, discloses the process for preparing amino alcohols by taking the following alpha-amino ketone;



where R = H (3b), Table 1, entry 4 page 748, and using a hydrogenation process with the catalyzed by ligand (2S,4S)-MCCPM 1a complexed to $[\text{Rh}(\text{COD})\text{Cl}]_2$, with effective results.

**Ascertainment of the Difference Between the Scope of the Prior Art
and the Claims (MPEP §2141.012)**

Helmechen lacks the express teaching of using an amino ketone which is a 1-butanone or an amino ketone which is a 1-propanone. It is for this reason the Examiner combined the teachings of the references of Sakurba 92 and Sakurba 95. Sakurba 92 discloses a dimethyl amine at the alpha position the use of ligand (R)(S)-BPPFOH complexed to a transition metal $[\text{Rh}(\text{COD})\text{Cl}]_2$. Sakurba 92 states that this reaction was not successful for the production of the alpha amino alcohol. However, Sakurba 95 used a methyl amine at the alpha position with a bisphosphine ligand with successful production of an amino alcohol with which has the form of an alpha amino ketone that was a 1-propanone.

**Finding of Prima Facie Obviousness Rational
(MPEP §2142-2143)**

It is known in the art that amino alcohols are important intermediate for chiral synthesis of biologically active substances. It is also recognized in the art at that one of

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the most convenient methods of preparation of optically active amino alcohols is the asymmetric hydrogenation of prochiral amino ketone catalyzed by chiral bisphosphine ligand-rhodium(I) complex. Therefore, it is desirous to develop a process for high yield production of amino alcohols from amino ketones using the rhodium complexed to other phosphine ligands.

The process of Helmchen et al. of producing amino alcohols with 100% yield for entries 6 and 7 using a rhodium salt complexed to the ligand (R)(S)-BPPFOH. The process of Sakurba 92 had no success using a ketone with a dimethyl amine functional group in the reaction involving the ligand (R)(S)-BPPFOH complexed to a transition metal $[\text{Rh}(\text{COD})\text{Cl}]_2$. However, in further experimentation as shown in Sakurba 95, amino alcohol was obtained at a yielded 79.8% in a reaction involving a amino ketone with a methyl amine functional group with a bisphosphine ligand complexed to a transition metal $[\text{Rh}(\text{COD})\text{Cl}]_2$.

In light of the success of hydrogenation reactions using an amino ketone with a methyl amine functional group, catalyzed by rhodium salt complexed to the ligand (R)(S)-BPPFOH, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use a hydrogenation process to prepare an alpha amino alcohol from an alpha amino ketone that was a 1-propanon or 1-butanone, and catalyzed by a transition metal such as $[\text{Rh}(\text{COD})\text{Cl}]_2$, complexed to a ligand such as (R)(S)-BPPFOH as suggested by Sakuraba 92 in view of the success of Sakuraba 95, to produce the process of the instant invention.

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In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common senses. In this instance the fact that a combination was obvious to try might show that it was obvious under §103. KSR, 550 U.S. at ___, 82 USPQ2d at 1397.

Claim Objections

11. Claim 1 is objected to because of the following informalities: at line 11, there appears to be a typographical error in "NHCOR₂" where the 2 is a subscript and should be a superscript. Appropriate correction is required.

Allowable Subject Matter

12. Claim 8 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims, as it relates to the R1 = a heterocyclic as elected.

13. Claim 9 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims, as it relates to the R1 = a heterocyclic as elected.

14. The process of claim 1 contains allowable subject matter where n = 2, 3 and ligand A and ligand B are as defined in claim 1.

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15. The process contains allowable subject matter because none of the references teach the process for preparing the amino alcohol from the enantioselective hydrogenation reaction of an amino ketone, where R1 is a heterocyclic as defined by applicant's claim 1, with and alpha amino ketone being a 1-propanone, 1-butanone, or 1-pentanone using a transition metal complex which is a rhodium or salt of rhodium, in which the transition metal is complexed to ligand A as defined by claim 1 of Applicant's process.

16. **No claims are allowed.**

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yate K. Cutliff whose telephone number is (571) 272-9067. The examiner can normally be reached on M-TH 8:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (571) 272 - 0871. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Yaté K. Cutliff
Patent Examiner
Art Unit 1609, Group
Technology Center 1600



SAMUEL BARTS
PRIMARY EXAMINER
GROUP 1600